Multilayered Transmucosal Therapeutic System

The invention relates to a multilayered film-shaped therapeutic system for transmucosal administration of active substances, especially of medicinal substances. These systems are suitable for rapid delivery of active substances over a prolonged period in a controlled manner.

Mucoadhesive medicament forms are known in the state of the art for example in the form of mucoadhesive tablets, disks or film-shaped administration forms. Some of those medicament forms are already available on the market. Mucoadhesive medicament forms are applied to the mucosa, especially to the oral mucosa (buccal and/or gingival mucosa), thereby enabling the delivery of the active substance contained therein and absorption via the mucosa. It is of advantage here that the active substances enter the circulation quickly and a quick onset of action can be achieved. Medicament forms of this kind are suitable, in particular, for administering such active substances as are only poorly absorbed from the gastrointestinal tract and/or exhibit a short plasma half-life.

The best known mucoadhesive administration forms are tablets which are configured in two layers and consist of a mucoadhesive layer and a retarding backing layer (Aftab®, Rottapharm). There have been endeavours to improve the functional capability of such mucoadhesive tablets, for example by providing drainage notches which are to enable that saliva liquid is transported away from the application site. Such tablet systems are indeed capable of fulfilling their function, but they are experienced as unpleasant to the patients since they are relatively thick, hard and inflexible, and thereby induce a marked foreign body sensation.

Apart from the above, mucoadhesive "disks" are known which can be formulated on the basis of lipophile, insoluble polymer matrices and hydrophile mucoadhesive polymers and, if required, surfactants. These disks usually have a thickness of approx. 1 mm and therefore cause an unpleasant foreign body-sensation in the mouth.

From US 4 713 243 there are known mono- or multilayered mucoadhesive films whose mucoadhesive layer consists of hydroxypropyl cellulose, an ethylene oxide homopolymer, a water-insoluble polymer (e.g. ethyl cellulose, propyl cellulose, polyethylene, polypropylene) and a plasticizer. These administration forms are considered more pleasant by the patients, but their usefulness is highly restricted on account of the only short period of adhesion. This short duration of adhesion is due to the fact that the polymers employed are readily soluble in water, so that no appreciable retardation of adhesion does occur. To achieve that the mentioned mucoadhesive films adhere to the mucosa for a prolonged period of time, the content of water-insoluble polymer components (e.g. ethyl cellulose, propyl cellulose) in the formulation must be increased. However, as a consequence the mucoadhesive systems thus produced have a greater thickness, which increases the foreign body sensation during the period of application. In addition, the greater thickness entails a decrease in the release of active substance since the diffusion paths become longer and the diffusion coefficients diminish.

It has also been proposed (US 5 719 197) to improve the coherence of mucoadhesive systems by using clay as additive. However, such clays must be regarded as disadvantageous because of their property of adsorbing certain active substances or of affecting the active substance stability by

catalytic effects. Furthermore, the weight and thickness of the system is markedly increased by these additives.

The task underlying the invention was thereby to provide mucoadhesive administration forms which do not have the above-mentioned disadvantages, in particular inducement of a foreign body sensation, insufficient active substance release and too short a duration of adhesion.
Furthermore, these mucoadhesive medicament forms are to enable a quick onset of action on the one hand and on the other hand enable a continuous and controlled active substance delivery over a prolonged period of time.

This task is solved, surprisingly, by film-shaped, at least double-layered transmucosal therapeutic systems according to claim 1 and by the preferred embodiments described in the dependent claims.

According to claim 1, the inventive therapeutic systems which are suitable, in particular, for transmucosal administration of active substances have a structure of at least two layers which are connected with each other. At least one of these layers contains active substance. One of the two sides of the inventive system is limited by a mucoadhesive layer which optionally contains active substance or is free of active substance. During application, this mucoadhesive layer is in contact with the absorbing mucosa, e.g. oral mucosa. The mucoadhesive layer of the system is connected with a backing layer which is mono-layered or double-layered and which may serve as active substance reservoir. A special property of the mucoadhesive layer consists in the fact that it is capable of swelling in aqueous media, but insoluble or only poorly, i.e. slowly, soluble therein. The insolubility or reduced solubility increases the period of adhesion to the mucosa, thereby enabling an active substance release that lasts for a prolonged period

of time. Since the inventive systems are film-shaped and preferably have a thickness of less than 1 mm, they do not cause a foreign body sensation and are not felt to be unpleasant by the patients, whereby the acceptance of such medicament forms is improved.

The term "aqueous media" is understood to mean, besides water, in particular physiological liquids, especially saliva.

The mucoadhesive layer consists mainly of a polymer mixture which is film-forming, swellable in aqueous media but non-soluble or only poorly soluble therein. The polymer mixture comprises at least one hydrophile, mucoadhesive polymer embedded or dispersed in a polymer matrix. Optionally, the mucoadhesive layer may contain active substance(s) or additives.

The aforementioned hydrophile polymer, respectively the hydrophile polymers is/are preferably selected from the group comprising hydrophile adhesive polymers carrying carboxyl groups, polyacrylates or polyacrylic acid derivatives (e.g. Carbopol® types, from the firm of B.F. Goodrich) and their salts, carboxymethyl cellulose and its salts, poly(methyl vinyl ether maleic anhydride) and its aqueous or alcoholic hydrolysates and salts (e.g. Gantrez® types, such as Gantrez-AN, -S, -ES, -MS; from ISP).

The above-mentioned polymer matrix of the mucoadhesive layer is essentially based on polymers which are hydrophile, but insoluble or slowly soluble in aqueous media. This polymer or these polymers is/are preferably selected from the group of polyvinyl alcohols and polyacrylates. Other polymers known to those skilled in the art which enable an anchorage of the mucoadhesive layer on the adjacent

backing layer that is durable in dry condition or in aqueous environment, may also be utilized.

To ensure a durable connection between the mucoadhesive layer and the backing layer superimposed thereon (respectively one of the individual layers of the backing layer, in the case of a multi-layered backing layer) it is advantageous to select base polymers which are identical with those polymers employed for preparing the backing layer, or are at least chemically allied thereto.
It is generally preferred for neighbouring layers of the film-shaped system to contain one or more identical or chemically allied base polymers which are preferably selected from the group of the polyacrylates.
In this way it can be ensured that for the period of application the mucoadhesive layer remains durably connected with the backing layer even in aqueous environment (oral cavity).

According to a preferred embodiment, the polymers of the mucoadhesive layer are crosslinked by employing physical or/and chemical methods. By cross-linking, the degree of solubility can be reduced without affecting hydrophilicity. In this way it is possible to additionally, and with particular advantage, further improve the duration of adhesion to the mucosa. Suitable crosslinking reagents and crosslinking processes are known to those skilled in the art (e.g. use of aluminium acetylacetonate or titanyl acetylacetonate as crosslinking agent).

The mucoadhesive layer may contain additives suitable for modulating the adhesive properties, these are known to those skilled in the art.

The backing layer or (in the case of a multilayer backing layer) the individual layers of the backing layer is/are

preferably produced on the basis of polyacrylates, especially on the basis of neutralised polymethyl methacrylates (e.g. Eudragit® E 100, Eudragit® NE 30 D, Plastoid® B; Röhm Pharma). Especially preferred are polyacrylates which are capable of swelling in aqueous media - largely independently of the pH value -, but are not soluble therein. The backing layer or at least one of the layers forming the backing layer may optionally contain one or more auxiliary substances, preferably selected from the group of the plasticizers, penetration enhancers, solubilizers, colorants, pigments and matrix formers. Suitable substances are known to those skilled in the art.

Suitable as plasticizers are, for instance, plasticizers from the group comprising hydrocarbons, alcohols (especially higher alcohols such as dodecanol, undecanol, octanol), polyhydric alcohols, polyethylene glycols, triglycerides, carboxylic acids, derivatives of carboxylic acids, ethers, esters (e.g. diethyl phthalate, n-butyl adipate, citric acid esters) und amines.

Suitable as absorption or permeation enhancers are, in particular, substances selected from the group comprising the following substances and substance classes: saturated or unsaturated fatty acids, fatty acid esters, especially esters with methanol, ethanol or isopropanol (e.g. oleic acid ethyl ester, oleic acid methyl ester, lauric acid methyl ester, lauric acid ethyl ester, adipic acid methyl ester, adipic acid ethyl ester), straight-chain or branched fatty alcohols and esters thereof, especially esters with acetic acid or lactic acid (e.g. ethyl oleate, ethyl laurate, ethyl palmitate, ethyl lactate, propyl lactate, propyl palmitate, propyl laurate, propyl oleate), polyhydric aliphatic alcohols or polyethylene glycols, sorbitan fatty acid esters and their derivatives obtained by ethoxylation, fatty alcohol ethoxylates, polyoxyethylene fatty acid es-

ter; lauric acid diethanolamide, oleic acid diethanolamide, coconut fatty acid diethanolamide, D-alpha-tocopherol, lauric acid hexyl ester, 2-octyldodecanol, dexpanthenol, isopropylidene glycerol, transcutol (= diethylene glycol monoethyl ether), DEET (= N,N-diethyl-m-tolueneamide), solketal, ethanol, 1,2-propanediol or other short-chain alcohols (e.g. alcohols with up to 6 C atoms), as well as menthol and other essential oils or components of essential oils. To optimize active substance flow, it is also possible to use combinations of two or more enhancers.

The total constituent amount of plasticizers and permeation-enhancing substances may be up to 10%-wt, relative to the film-shaped medicament form. Particularly preferred is a content of less than 5%-wt., especially less than 1%-wt.

Examples for solubilizers are polyhydric alcohols such as 1,2-propanediol, butanediol, glycerol, polyethylene glycol 400, tetrahydrofurfuryl alcohol, diethylene glycol monoethyl ether, diethyl toluamide and monoisopropylidene glycerol. The portion of the solubilizers(s), relative to a medicament form, can be between 0.1 and 10%-wt, preferably 0.5 to 5%-wt.

Suitable as pigments are, in particular, talcum, titanium dioxide, iron oxide or lamellar pigments. The pigment portion can amount to up to 80, preferably up to 70%-wt, relative to the polymer portion in the respective layer.

The inventive film-shaped mucoadhesive systems are constructed, in the simplest case, of two layers, namely a mucoadhesive layer and a backing layer connected therewith, which backing layer may serve as active substance reservoir (Fig. 1). In addition, the mucoadhesive layer may also contain active substance, preferably the same active substance as contained in the backing layer.

The active substance release from the system to the mucosa takes places by diffusion from the layers of the system.

According to a preferred embodiment, the backing layer is modified by suitable additives in such a manner that the permeation of water and the diffusion of active substance in this layer is reduced or blocked, relative to the diffusion and permeation in the mucoadhesive layer.

In further embodiments of the invention it is provided for the systems to be designed as multilayer systems and preferably to contain up to 6 individual layers, with a layer number of 2 to 4 being preferred. In each case, one of the surfaces of the system is formed by a mucoadhesive layer. Preferably, all of the layers contain the same active substance, at the same or different concentrations.

The multilayered structure enables the manufacture of inventive systems which immediately after application release an initial burst dose and subsequently release a maintenance dose at a reduced delivery rate over a prolonged period of time (several hours, preferably 0.5 to 24 hours).

Especially advantageous are embodiments wherein the backing layer is constructed of two or more individual layers which are superimposed one upon another and are connected with one another. In this way it is possible to increase the active substance dose contained in the system. In addition, the individual layers may contain additives which modify the solubility and the diffusion coefficient of the active substance in the respective layer. Thereby, a multilayer is obtained which has a defined concentration gradient. This embodiment is particularly advantageous. The formation of a concentration gradient can in addition be assisted by providing the active substance in the individual layers in increasing or decreasing amounts or concentrations.

According to a further preferred embodiment it is provided that the backing layer or that outer layer which is located on the side of the system that is opposite the mucoadhesive layer and there forms the outer surface is modified by suitable additives such that the permeation of water and the diffusion of active substance in this layer is reduced or blocked, relative to the diffusion and permeation in the mucoadhesive layer or in the other layers of the backing layer.

In this manner, a transmucosal system is obtained which has a structure of at least three layers, namely comprising a mucoadhesive layer, at least one middle reservoir layer connected thereto, and an outer layer or boundary layer connected with said reservoir layer (Fig. 2). In the latter layer, the diffusion of active substance - relative to the middle layer(s) - is reduced or even completely blocked.

The modification of the diffusion and permeation properties can be brought about, in particular, by varying the pigment content or/and by admixing suitable diffusion-retarding polymeric (e.g. ethyl cellulose, propyl cellulose) or non-polymeric auxiliary substances. In this manner, it is possible to adjust the diffusion properties of the backing layer, respectively the outermost layer of the backing layer, between two extremes, namely between complete blockage of the diffusion on the one hand, and practically unimpeded or unmodified active substance diffusion from the matrix. Thus it is possible to optionally manufacture systems which release the active substance(s) on one side (i.e. only on the mucoadhesive side) or on two sides (i.e. on the mucoadhesive side and on that side of the system which is opposite thereto).

At least the middle layer(s) of the system contain(s) active substance; preferably, also the aforementioned outer boundary layer contains the same active substance(s). In addition, the mucoadhesive layer may also contain active substance.

With the above described, at least three-layered structure comprising the said outer layer, a system is obtained wherein the delivery of active substance is controlled by a combination of matrix-controlled diffusion and membrane-controlled release.
Generally such a system, which is based on a mixed control (combination of matrix and membrane control) would release the active substance in a kind of saturation function, i.e. the delivery rate of the system would decrease further and further as the exhaustion of the system increases. By a suitable formulation, especially by a suitable selection of the matrix polymer(s) (increasing the portion of hydrophile functional groups), or by adding suitable hydrophile, water-binding additives (especially polyalcohols or polymeric surfactants with high HLB value, preferably HLB ≥ 10, especially HLB ≥ 15), it is possible to influence and increase the degree of water uptake or the degree of swelling of the reservoir layer with increasing retention time of the system in the moist medium (i.e. at the application site in the oral cavity).

By means of the above-described measures the diffusion coefficient in the reservoir layer can be increased by an increase in the swelling or by an increase in the degree of hydration. It is thereby possible to compensate the decrease in the release rate, caused by the decrease of the concentration gradient, by an increase in the swelling and hydration of the active substance matrix such that a re-

lease results which is essentially linear, this is accompanied by a high exhaustion of the system.

These properties of the systems according to the invention are of significance especially with a view to a prolonged application of the system, for instance over a period of several hours (e.g. 2 to 24 h). This is true, in particular, where the substances to be administered have a correspondingly narrow therapeutic window.

At least one of the layers of the inventive film-shaped systems contains an active substance or a combination of active substances. The polymers of the individual layers form a polymer matrix which may serve as active substance reservoir. In this polymer matrix the active substance(s) are already contained, in dissolved, suspended or emulsified form, preferably "dissolved" in the sense of a "solid solution". Suitable as active substances are, in particular, medicinal substances, with particular preference highly efficacious medicinal substances, e.g. from the following groups: agents acting on the nervous system, psychopharmacological agents, sedatives, narcotics, hormones, insulin-like active agents, analgesics, anticonvulsives, anti-parkinson agents, medicaments acting on the cardiovascular system, anti-infectives, active agents for treating metabolic disturbances (e.g. lipid-lowering agents), agents acting on the muscular system, and others.
The inventive systems are suitable above all for administering medicaments that are subject to rapid metabolism or/and are absorbed only insufficiently via the gastrointestinal route.
The invention will be explained in more detail in the following by means of examples and drawings.

Fig. 1 and Fig. 2 show, in schematic cross-section, the structure of layers of two examples of mucoadhesive systems (1) according to the invention.

Fig. 1 shows a system (1) with a double-layered structure comprising a mucoadhesive layer or adhesive layer (2) and a backing layer or reservoir layer (3) connected therewith. The mucoadhesive layer (2) of the system (1) represented is in adhesive contact with a mucosa (4); status during application.

Fig. 2 shows a system (1) with a three-layered structure comprising a mucoadhesive layer (2) and a backing layer (3), which backing layer (3) consists of two individual reservoir layers (3a, 3b), namely a middle layer (3a) and an outer layer or boundary layer (3b). The reservoir layer (3b), closing the system towards the outside, is preferably configured so as to be diffusion-controlled.

Example

Preparation of a three-layered system (as in Fig. 2)

An active substance is dissolved in a neutral polyacrylate (e.g. Eudragit® NE 30 D; Röhm), either directly or employing a suitable solvent known to those skilled in the art, if need be by using a dissolving intermediary or solubilizer. The selection of the suitable method is dependent on the solubility, respectively the dissolving properties of the active agent employed.
Furthermore, an appropriate pigment is added to the active substance-containing polymer solution, e.g. talcum, TiO_2, iron oxide or lamellar pigments, and a homogenous liquid is prepared. The pigment content is relatively high and is at approx. 60%-wt, relative to the polymer portion.

Subsequently, the viscosity of the liquid is adjusted such that it is suitable for the subsequent processing steps. The liquid is applied, preferably by means of a casting method or spraying method, to an inert support and is subjected to subsequent drying, which results in a thin film. The inert support employed must be such that the film remains adhering thereto after drying, but can be detached from the support without being destroyed.

In the same manner as above-described a second liquid is prepared which differs from the first formulation only in that it does not contain the pigment or contains a lower portion of pigment. Thereby, the active substance content is increased relative to the entire solids content, as compared to the liquid prepared first. The second liquid is coated, again by means of a spraying or casting method, onto the layer prepared first and is subsequently dried so that a two-layer laminate with two reservoir layers is obtained.

To prepare the mucoadhesive layer, an aqueous solution of highly hydrolysed polyvinyl alcohol (e.g. Mowiol 28-99, Clariant) of suitable concentration (e.g. 10%-wt.; optionally 0.5 to 60%-wt) is prepared, and a suitable portion of adhesive polymer (e.g. Gantrez S 95; ISP) is dissolved therein. The portion of adhesive polymer in this example corresponds to the polyvinyl alcohol portion (that is, mixing ratio 1:1; weight content). But other mixing ratios can be employed as well, e.g. in the range of 50:1 to 1:50, relative to the portion of adhesive : the portion of polyvinyl alcohol).
The resultant homogenous solution is coated, again employing a suitable application method, onto the previously prepared two-layer laminate, and subsequently dried.
This yields a three-layer laminate which - depending on the coating weight - is approx. 50 to 250 µm in thickness. The

top side of this laminate has good tackiness in moist state and has mucoadhesive properties. The laminate as a whole has very good flexibility and adheres to a mucosa for several hours after application thereof.

The inventive transmucosal systems are advantageously suitable for administering active agents, especially medicaments, for therapeutic or prophylactic treatment in human or veterinary medicine.